Does Anti-Vascular Therapy Reprogram the Immunosuppressive Microenvironment in Gastric Cancer?

J Tokyo Wom Med Univ 89(Extra1): E100-E109, 2019 Jul

Review

Does Anti-Vascular Therapy Reprogram the Immunosuppressive Microenvironment in Gastric Cancer?

Shuji Kitahara[1] and **Yasuhiro Suzuki**[2]

[1]Department of Anatomy and Developmental Biology, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan
[2]Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

(Accepted August 24, 2018)

Abnormal cell proliferation, a characteristic of malignant tumors, is accompanied by angiogenesis, through a complex molecular pathway involving various vascular growth factor groups. The abnormal blood vessels formed by the cancer establish a hypoxic and low pH environment in the vicinity of the tumor, causing a decrease in immunogenicity. Since the cancer cells produce immunosuppressive factors that further induce the related cells, an immunosuppressive environment optimal for the growth of the tumor is established. Although the gastrointestinal tract maintains homeostasis by specific immune surveillance mechanisms involving the lymph nodes and Peyer's patch, once a malignant tumor develops, a system that escapes the monitoring mechanism by taking advantage of the immune-checkpoint route is newly generated. Although normalization of the tumor microenvironment using molecular target drugs has attracted attention in recent years as the next generation cancer treatment, it is reported that this method also affects the host immune mechanism simultaneously. However, since many aspects of this intervention including the detailed mechanism of the immune mechanism for tumor microenvironment normalization, the prognosis, and the side-effects are still unclear, the clinical applications are not feasible yet. We believe that "normalization of the tumor environment and tackling its mechanism," can construct a host environment that maximizes the therapeutic effect of anti-cancer therapies including chemotherapy, immunotherapy, and radiation therapy, in addition to restoring the host immunity of the gastrointestinal tract. In other words, this could become the next generation cancer treatment. This review article focuses on tumor angiogenesis, tumor microenvironment, and the specific immune surveillance mechanism of the gastrointestinal tract, and finally proposes what is necessary for the "reprogramming of tumor microenvironment".

Key Words: tumor blood vessel, tumor microenvironment, immunotherapy, gastric cancer

Introduction

Gastric cancer (GC) is the third most common cancer with the second highest mortality rate worldwide, with one million new patients diagnosed every year.[1] The vast majority of GC are adenocarcinomas, which can be subdivided into intestinal and diffuse types according to the Lauren classification.[2] Tumor microenvironment processes such as angiogenesis, fibrosis, and inflammation are critical for the local progression and metastasis of solid tumors, including those occurring in gastrointestinal cancer.[3] These processes create a tumor microenvi-

Corresponding Author: Shuji Kitahara, Department of Anatomy and Developmental Biology, School of Medicine, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. skitahara@twmu.ac.jp

doi: 10.24488/jtwmu.89.Extra1_E100

ronment characterized by hypoxia, which suppresses the immune system's ability to fight the cancer. As a consequence, no single chemotherapy agent or combination regimen consistently leads to objective tumor shrinkage, and novel treatment strategies for GC are desperately needed.[3]

The tumor vasculature is an essential component of the tumor microenvironment, influencing tumor behavior and treatment response. It can be targeted specifically using anti-angiogenic drugs.[4-6] Tumor blood vessels are histopathologically different from normal blood vessels. They have irregular shape, diameter, and branching patterns and cannot be classified as arterioles, venules, or capillaries.[7] Their endothelial cells are interconnected loosely with abnormal pericytes (decreased pericyte coverage) that are responsible for their leaky nature. When compared to normal blood vessels, tumor vessels appear immature. Angiogenesis is not just dependent on endothelial cell invasion and proliferation, but also requires the pericyte coverage of vascular sprouts for stabilization and maturation of vascular walls. This phenotype might be associated with structural aberrations in their basement membrane.[8]

Vascular abnormalities associated with the tumor may be attributed to the tumor microenvironment.[9] These abnormalities may contribute to the development of tumor resistance to conventional chemo-, radio-, and immune-based therapies. Dr. Jain[10] proposed that an appropriate anti-angiogenic treatment can lead to normalization of the tumor vasculature by reducing vascular permeability and interstitial fluid pressure, thus improving blood flow and tumor perfusion. A normalized vasculature can reduce hypoxia and enhance the delivery of oxygen and cytotoxic agents for radiation therapy, but also for anti-tumor immune response.[11] Preclinical and clinical studies have supported the hypothesis that anti-angiogenic therapy can normalize the tumor vasculature, at least transiently.[4]

On the other hand, tumor cells do not act alone. Malignant tumors develop a complex multifaceted relationship with the environment, and simply making them accessible may not be sufficient to produce vulnerability to treatment. The immune response of the host is critical to the success of an immunotherapy regimen, such as immuno-checkpoint inhibition.[4] However, the determinants of the response are not completely understood. Tumor infiltration by immune cells such as cytotoxic T-lymphocytes varies widely in density, composition, and clinical significance.[12]

Blood vascular and lymphatic endothelial cells play important roles in trafficking immune cells, controlling the microenvironment, and modulating the immune response. Improving access to the malignant tumor through vascular alteration with anti-angiogenic drugs may provide an effective combinatorial strategy for immunotherapy, and might be widely applicable to various tumor types, especially GC.[13] Moving forward, these insights may be useful for designing new approaches, for example by combining anti-angiogenic agents with immune-checkpoint inhibitors that will produce a substantial improvement in the overall survival of malignant GC patients. This review article focuses on the potential new approach to GC therapy.

Tumor Blood Vessels Can Modulate the Tumor Microenvironment

Tumor angiogenesis is a vital process in the progression and metastasis of solid malignant tumors. Angiogenesis within the tumor develops abnormal leaky blood vessels. It has been reported that tumor vessels can create microenvironments that are histopathologically distinct from normal vessels (**Figure 1, 2**).[14] Electron microscopy revealed that most tumor vessels in lung adenocarcinoma have deformed diameters (**Figure 2A**). In addition, the tumor endothelial cells have loose interconnections, intercellular openings, and abnormal pericytes, which are likely to be responsible for vessel leakiness. Moreover, the structural abnormalities in the basement membrane of tumor blood vessels are also responsible for their relative immaturity compared to normal blood vessels (**Figure 2B-E**). Accordingly, a tumor blood vessel has an abnormal blood flow and is excessively leaky. Insufficient blood flow to the tumor tissue leads to hypovascular areas, severe hypoxia, and necrosis.

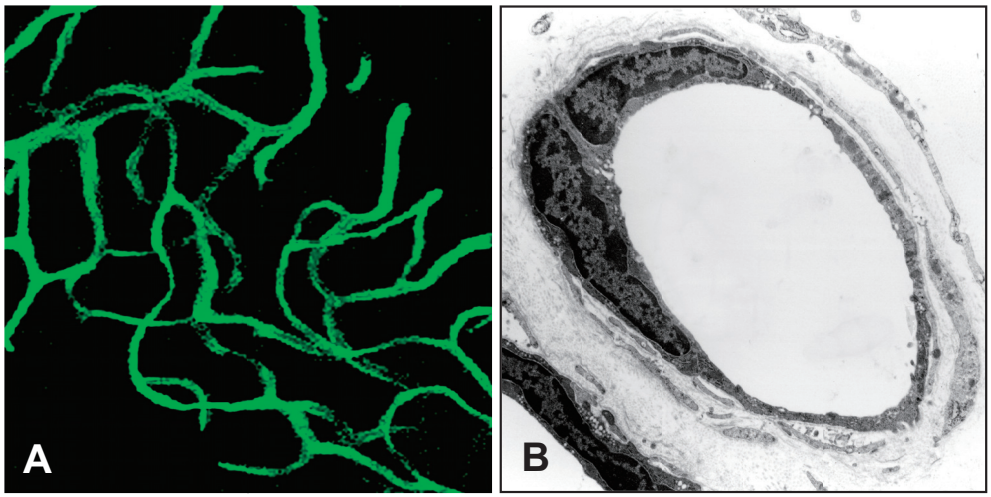

Figure 1 Normal blood vessels in mouse subcutaneous tissue have smooth endothelial cells.
A: Tomato lectin-labeled vascular architecture in normal mouse subcutaneous region.
B: Ultra-thin sections showing normal blood vessel in mouse subcutaneous tissue.

Although GC is a highly angiogenic cancer, it is characterized by hypoxia.[3] Hypoxia may promote GC growth and progression, and promote resistance to existing therapies. Conversely, inducing vessel normalization and alleviating hypoxia might delay GC progression and metastasis. Vascular endothelial growth factor (VEGF) is the key factor for the abnormal structure and function of tumor vessels.[14] One of the cues driving evasive resistance is increased hypoxia induced by anti-VEGF treatment. Strong inhibition of the VEGF pathway results in pruning of the tumor vasculature, which induces hypoxia in malignant tumors.[2] Tumor hypoxia leads to hypoxia-inducible factor 1 alpha subunit (HIF1α) stabilization, which induces hypoxia responsive genes including VEGF. Thus, VEGF treatment imposes a vicious cycle resulting in evasive resistance. We recently identified that the current treatment dose of sorafenib (anti-VEGF) can induce hypoxia in liver cancer, which resulted in infiltration by immune-suppressive leukocytes.[2,15] Based on these results, we hypothesize that dose titration of selective anti-angiogenic agents is warranted to optimize treatment and elicit anti-tumor immunity. Founded on the above considerations, if we can control tumor angiogenesis and normalize tumor blood vessels, the tumor microenvironment in GC may improve to allow anti-tumor immunity.

Why Target the Immune Checkpoints in GC?

Cancer immunotherapy has shown great promise to transform clinical oncology in a radical way by substantially improving outcomes in certain advanced malignant cases. However, in most patients, the immune-suppressive microenvironment interferes with the development of an appropriate anti-tumor immune response. Co-inhibitory antigen presentation signals, called immune checkpoints, are often activated in the malignant tumor tissue, which results in the evasion of host immunity.[16] Based on the success of blocking programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) in melanoma, targeting an immune-checkpoint is an emerging strategy that is gaining significant interest for malignant cancer therapy.[17] Anti-immune-checkpoint therapy is ideal for GC patients for at least three reasons. First, GC (especially virus-induced GC) is immunogenic, but the immune response is suppressed by multiple mechanisms. This suggests an anti-immune-checkpoint blockade could be effective.[1] Second, gastric cancers have vascular abnormalities that lead to hypoxia, fibrosis, and immune suppression. Modulating these processes with anti-angiogenic therapy could potentially shift the tumor microenvironment toward promotion of an anti-tumor response.[18] Finally, gastrointestinal cancer is particularly prone to chronic inflam-

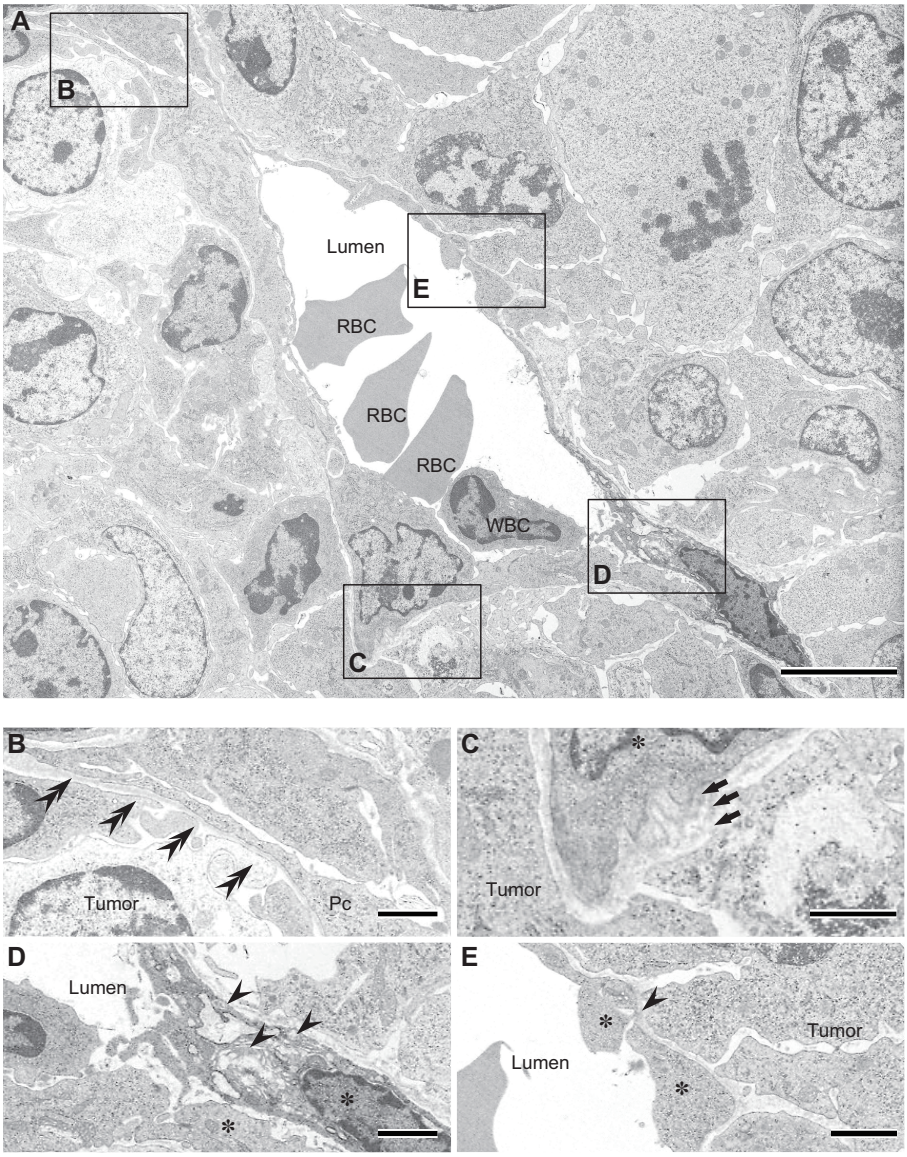

Figure 2 Electron micrograph of metastatic adenocarcinoma showing the morphological changes to tumor blood vessels in gastrointestinal cancer.
A: Ultra-thin sections showing tumor blood vessel abnormalities in mouse intestinal tumor. Tumor vessel irregularities included basement membranes.
B-E: Higher magnifications of (A). Abnormal endothelial cells with long protuberances (B, double arrowheads). Note the multi-layered basement membranes (C, arrows). Abnormal endothelial cells are loosely interconnected (D, arrowheads) and have intercellular openings (E, arrowhead). Asterisks, endothelial cell. Arrows indicate basement membrane. Scale bars: 10 μm (A), 2.5 μm (B-E).

mation, which can create an immune-suppressive microenvironment.

Despite its wide use in the clinic, chemotherapy has limited efficacy and high toxicity. Clearly, new systemic treatment approaches that are more efficacious and less toxic − such as low dose anti-angiogenic therapy combined with immunotherapy − are desperately needed. Our preliminary data showed that the inhibition of tumor angiogenesis factor (vasohibin2) could improve the chronic inflammation in gastrointestinal cancer (**Table 1**, **Figure 3**: The $Apc^{Min/+}$ mouse spontaneously develops multiple intestinal adenomas that clinically mimic those observed in patients with familial adenomatous polyposis and undergo early transformation into adenocarcinomas. In addition, $Apc^{Min/+}$ mice of a

Table 1 Microarray analysis showing downregulation of genes in $Apc^{Min/+}/Vash2^{-/-}$ mice compared with $Apc^{Min/+}$ mice.

Down-regulated genes in $APC^{min}/VASAH2^{-/-}$	
Il6	Mus musculus interleukin 6 (Il6), mRNA [NM_031168]
Eif2s3x	Mus musculus eukaryotic translation initiation factor 2, subunit 3, structural gene X-linked (Eif2s3x), mRNA [NM_012010]
Retnlg	Mus musculus resistin like gamma (Retnlg), mRNA [NM_181596]
Cd163 l1	Mus musculus CD163 molecule-like 1 (Cd163 l1), mRNA [NM_172909]
Xlr3b	Mus musculus X-linked lymphocyte-regulated 3B (Xlr3b), mRNA [NM_001081643]
Il11	Mus musculus interleukin 11 (Il11), mRNA [NM_008350]
S100a8	Mus musculus S100 calcium binding protein A8 (calgranulin A) (S100a8), mRNA [NM_013650]
Igh-VJ558	M.musculus VH mRNA (VH5) [X73076]
Gm5106	PREDICTED: Mus musculus predicted gene 5106 (Gm5106), misc_RNA [XR_168418]
Ceacam10	Mus musculus carcinoembryonic antigen-related cell adhesion molecule 10 (Ceacam10), mRNA [NM_007675]
Pappa2	Mus musculus pappalysin 2 (Pappa2), mRNA [NM_001085376]
Tmem190	Mus musculus transmembrane protein 190 (Tmem190), mRNA [NM_030028]
Il22ra2	Mus musculus interleukin 22 receptor, alpha 2 (Il22ra2), mRNA [NM_178258]
Hsd3b2	Mus musculus hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2 (Hsd3b2), mRNA [NM_153193]
Ereg	Mus musculus epiregulin (Ereg), mRNA [NM_007950]
Padi4	Mus musculus peptidyl arginine deiminase, type IV (Padi4), mRNA [NM_011061]
Padi4	Mus musculus peptidyl arginine deiminase, type IV (Padi4), mRNA [NM_011061]
Cxcl13	Mus musculus chemokine (C-X-C motif) ligand 13 (Cxcl13), mRNA [NM_018866]
Hsd3b3	Mus musculus hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 3 (Hsd3b3), transcript variant 1, mRNA [NM_001161742]
Ighg	Mus musculus Immunoglobulin heavy chain (gamma polypeptide), mRNA (cDNA clone MGC: 102659 IMAGE: 4015795), complete cds [BC092269]
Mmp13	Mus musculus matrix metallopeptidase 13 (Mmp13), mRNA [NM_008607]

Microarray analysis showed that epiregulin and the IL-6 family (IL-6 and IL-11) were downregulated in the tumors of $Apc^{Min/+}/Vash2^{-/-}$ mice compared with control mice.

pure C57BL/6 background were mated to $Vash2^{-/-}$ mice of a mixed C57BL/6 background, and the resulting pups were screened for the Min mutation and for the $Vash2^{-/-}$ gene by PCR). These results indicate that the combination of anti-angiogenic therapy and immunotherapy (such as immune-checkpoint inhibition) is an effective treatment for GC.

How Does Gastrointestinal Cancer Evade Host Immunity?

The majority of gastric cancers are associated with infectious agents, including the *Helicobacter pylori* bacterium and Epstein-Barr virus (EBV).[19] Recently, The Cancer Genome Atlas (TCGA)project reported that PD-L1 expression is elevated by 15% in EBV-positive gastric cancers. An evaluation of the messenger RNA (mRNA) revealed elevated expressions of Janus kinase 2 (JAK2), PD-L1, and programmed cell death 1 ligand 2 (PD-L2).[1] In addition, Lin et al.[20] reported that non-Asian GC was significantly enriched in signatures related to T-cell biology, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) signaling. Similarly, in the tissue microarray (TMA)cohorts, non-Asian GC showed significantly higher expression of T-cell markers and lower expression of the immunosuppressive T-regulatory (Treg) cell marker FoxP3. In lymphocyte-rich gastric carcinomas the stroma has even been termed a "tertiary lymphoid tissue".[21] However, GC usually evade immune surveillance. Multiple immune-suppressive mechanisms have been proposed.

The stomach is inherently "tolerogenic" to prevent aberrant immunity in response to potential antigens absorbed by the epithelium.[22] On the other hand, GC are inflammation-induced malignancies because they often occur in a diseased stomach with a background of gastritis.[23] The underlying chronic inflammation and viral infection create an immune-suppressive environment in the stomach through the production of cytokines including interleukin (IL)-6, IL-11, tumor necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β).[24,25] Our data also showed that the regulation of vasohibin2, an angiogenesis factor, could downregulate IL-6 and IL-11 (**Table 1**).

Another important mechanism of immune eva-

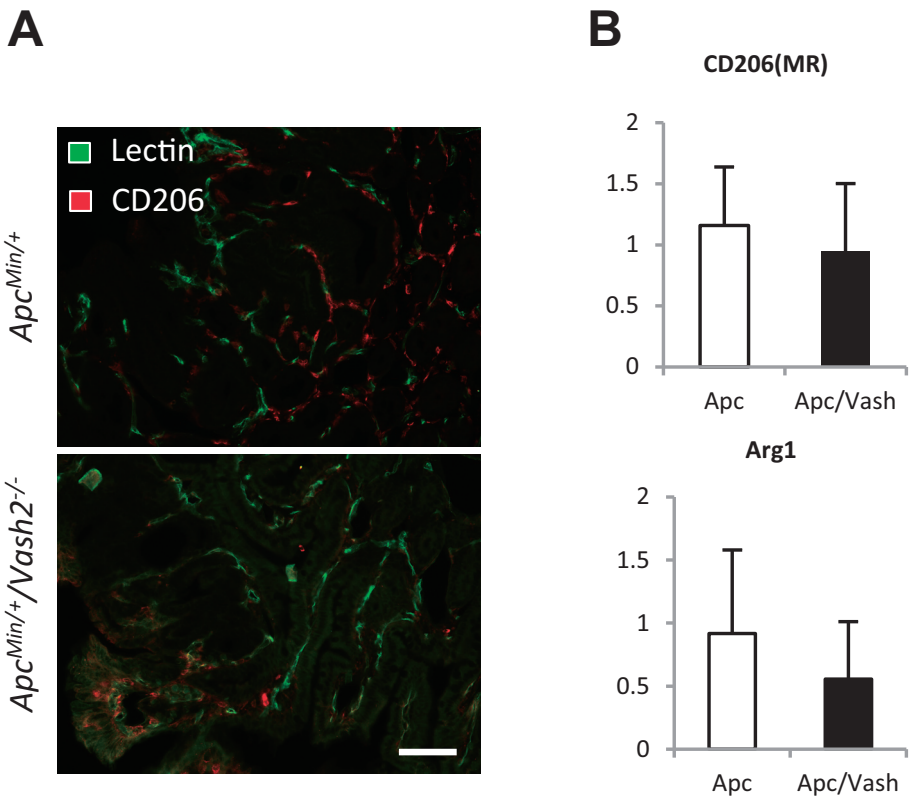

Figure 3 Inhibition of pro-tumor angiogenesis factor vasohibin2 changes the tumor microenvironment.

A: Double-immunostaining of tomato lectin and CD206 detecting M2 macrophage in a tumor of *Apc*$^{Min/+}$ mice and *Apc*$^{Min/+}$*/Vash2*$^{-/-}$ mice. The number of M2 macrophages trend toward an increase in response to vasohibin2 inhibition. Scale bar: 100 μm.

B: Gastrointestinal tumors of *Apc*$^{Min/+}$ mice and *Apc*$^{Min/+}$*/Vash2*$^{-/-}$ mice were examined for M1 and M2 like macrophage factor (CD206, Arg1) by qRT-PCR. The expression of Arg1 trend toward a decrease in *Apc*$^{Min/+}$*/Vash2*$^{-/-}$ mice.

sion in cancer involves infiltration of tumors by immune-suppressive leukocytes such as Tregs and myeloid-derived suppressor cells (MDSCs). Exhaustion of CD4 + T cells has also been reported as a mechanism of immune evasion in advanced cancer patients.[26,27] While the immune response to specific antigens is recognized by major histocompatibility receptors, co-stimulatory and co-inhibitory molecules regulate the intensity of the response. Immune checkpoints are co-inhibitory molecules that are physiologically expressed for the maintenance of self-tolerance.[28] In the GC microenvironment, immune-checkpoint molecules such as CTLA-4 and PD-L1 are overexpressed and broadly induce the evasive mechanism.

Anti-vascular Therapy Can Modulate the Immune Response

Reactivation of the immune response is key to overcoming treatment-resistant GC. Growing evidence is showing that combining anti-angiogenic therapy with immunotherapy in certain contexts may improve the immune response to solid cancers.[11,29] Several other studies have evaluated the change in immune response after anti-angiogenic therapy. For example, bevacizumab has been shown to enhance the proportion and function of dendritic cells (DC) in solid cancer patients[30]. In mouse models, it has been reported that an anti-VEGF antibody can enhance the number and function of DC.[31] Previously, Huang et al. [32] reported an interesting finding regarding the treatment dose of anti-angiogenic therapy in a mouse model of breast cancer. When anti-vascular

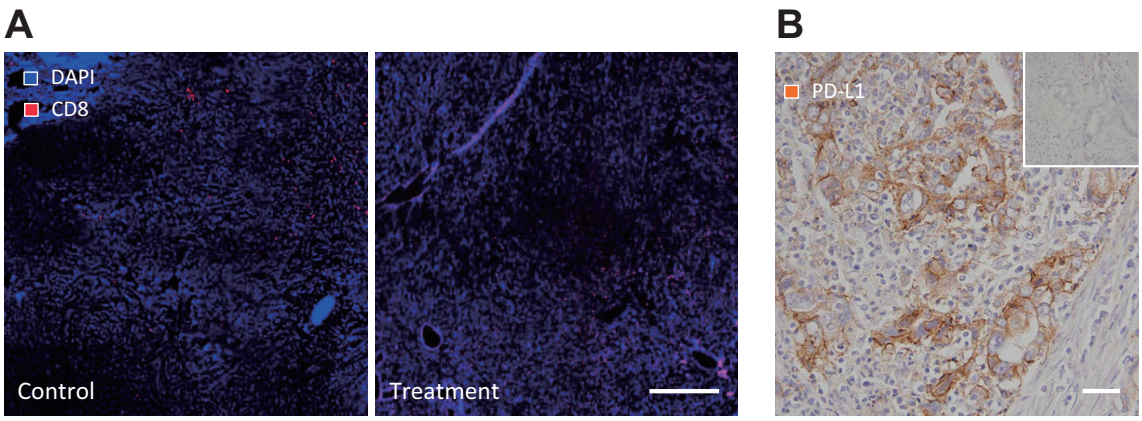

Figure 4 Anti-vascular therapy can modulate digestive tumor immune response.
A: Double-immunostaining of 4',6-diamidino-2-phenylindole (DAPI) and CD8. Lymphocytes infiltrated to the center of the malignant tumor. Right image - anti-angiogenic treatment model of mouse liver cancer. In the treatment model, CD8 positive lymphocytes infiltrated to the tumor center. Scale bar: 100 μm.
B: Immunostaining of PD-L1 in a human pathological gastrointestinal cancer sample. A substantial number of tumor cells expressed PD-L1 in the tumor area. The inset indicates a PD-L1 negative human sample. Scale bar: 100 μm.

endothelial growth factor receptor 2 (VEGFR2) neutralizing antibody was administered at a low dose, the structure of the tumor vasculature was normalized and anti-tumor immunity was promoted. Conversely, a high dose of anti-VEGFR2 neutralizing antibody induced vascular pruning and increased tissue hypoxia within the tumor. When they looked at the infiltrating leukocytes, the number of tumor-infiltrating macrophages increased while glucocorticoid receptor (Gr1) + cells decreased. Interestingly, the macrophages showed a decrease in M2 phenotype, suggesting an improvement in anti-tumor immune activity. Treg activity was also decreased in the low dose anti-VEGFR2 neutralizing antibody group compared to the high dose group. Our results concur with the M2 phenotype macrophage data **(Figure 3A, B)**. Recently, when we used therapeutic doses of sorafenib in liver cancer models, we detected increased hypoxia and an increase in Gr1 + cells, Tregs, and macrophages.[12,15] In addition, low dose anti-VEGFR2 neutralizing antibody could induce infiltration of cluster of differentiation (CD) 8 positive lymphocytes in liver cancer (**Figure 4A**). These experiments suggest a potential benefit on the immune response to GC with dose titrations of anti-VEGF therapy.

Immune-checkpoint Targeting Has Potential to Overcome the Immune-suppressive Environment

To overcome the immune-suppressive environment in GC, we have to focus on the immune-checkpoint blockade, especially on anti-PD-1/PD-L1 therapy. Numerous agents targeting PD-L1/PD-1 check point are in various phases of clinical development. However, the correlation between PD-L1 expression and the prognosis of solid tumors, such as GC, is controversial. Here, we propose new strategies to investigate the potential value of immune-checkpoint blockade and anti-angiogenic therapy in the prognostic prediction of GC.

PD-1 is a CD28 superfamily member that conveys co-inhibitory signals for T-cell receptors.[33] PD-1 is expressed in CD8 + T cells, Tregs, and MDSCs.[34,35] PD-1 also regulates peripheral tolerance and autoimmunity. Chronic exposure to antigen leads to the over-expression of PD-1 in T cells, which induces anergy or cell exhaustion.[36] Cancer cells can evade immune surveillance by hijacking PD-L1/PD-1 signaling. By expressing PD-L1 or PD-L2, PD-1 is activated in tumor-infiltrating lymphocytes, shutting down the immune response.[37] PD-1/PD-L1 expression can be detected in clinical samples and is significantly correlated with the stage of human GC **(Figure 4B)**, local recurrence rate, and poor progno-

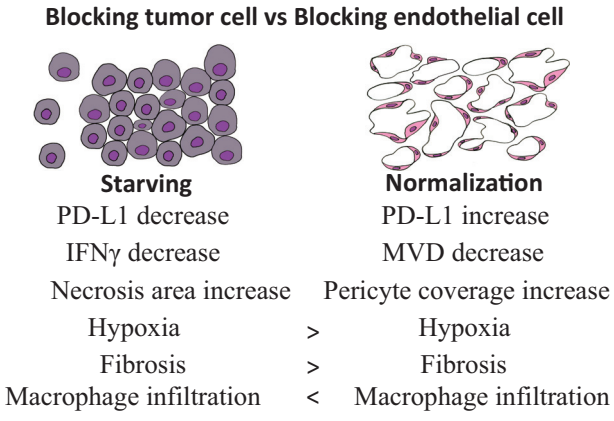

Figure 5 Targeting tumor VEGFR2 vs targeting endothelial cell VEGFR2.
Blocking VGEFR2 in endothelial cells could normalize tumor blood vessels and improve hypoxia and fibrosis compared to blocking VGEFR2 in tumor cells. Note that, single anti-tumor treatments were not efficacious in gastric cancer. Modulating these processes with anti-angiogenic therapy might potentially modify the immune microenvironment and promote anti-tumor response.

sis.[1] These data support the potential of anti-PD-1/PD-L1 therapy in GC.

Conclusion

We therefore propose that vascular normalization can improve an immune response against GC. The work to be performed will lay the groundwork for a new paradigm of immunotherapy that modulates the tumor microenvironment (**Figure 5**), and could rapidly impact clinical practice.[32]

Acknowledgements

We thank Mrs. Hiromi Sagawa and Mrs. Kae Motomaru of Tokyo Women's Medical University for their technical help. Special thanks go to Dr. Dan G Duda and the gastric cancer research team of Edwin L Steele Laboratories for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School and Yasufumi Sato of the Department of Vascular Biology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, and my colleagues from the Department of Anatomy and Developmental Biology, Tokyo Women's Medical University, Tokyo, Japan for their advice and expertise.

Conflicts of Interest: The authors declare no conflicts of interest associated with this manuscript.

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抗血管新生療法は胃がんにおける免疫抑制微小環境を改善できるか？

[1]東京女子医科大学医学部解剖学・発生生物学講座
[2]東北大学加齢医学研究所腫瘍循環研究分野
北原（キタハラ）　秀治（シュウジ）[1]・鈴木（スズキ）　康弘（ヤスヒロ）[2]

悪性腫瘍の特徴所見である異常細胞増殖には，様々な血管増殖因子群による複雑な分子経路を介した血管新生が伴う．癌の作る異常血管は，腫瘍周辺の低酸素，低 pH 環境などを作り出し，免疫原性の低下を引き起こす．癌細胞は免疫抑制因子を産生し，さらに関連細胞が惹起され，癌生育に最適な免疫抑制性環境が構築されていく．一方，消化管は，リンパ節，パイエル板といった特異的な免疫監視機構を有し恒常性を維持しているが，一旦悪性腫瘍が発生すると，免疫チェックポイント経路を利用した，監視機構を逃れるシステムが新たに構築される．近年，次世代の癌治療法として，分子標的治療薬を用いた腫瘍微小環境の正常化が注目されており，同時にこの方法が宿主免疫機構にも影響を与えることが報告され始めている．しかしながら，こうした免疫機構をはじめ，腫瘍微小環境正常化に至るまでの詳しいメカニズムや，正常化後の予後，副作用に関しては未だ不明な点が多く，現在も臨床応用は出来ていない．われわれは上記を背景とし，この「腫瘍微小環境の正常化，およびそのメカニズムへのアプローチ」が，結果として，消化管における強力な宿主免疫力を回復させると共に，化学療法，免疫療法，放射線療法などの治療効果を最大限に発揮させる宿主環境を構築する，つまり次世代の癌治療法としての可能性を確信している．本総説は，腫瘍血管新生，腫瘍微小環境，消化管の特異的な免疫監視機構に焦点をあて，最終的に「腫瘍微小環境のリプログラミング」を起こすためには何が必要かを提案する．